El estudio “ISAR-REACT 5” y sus implicaciones en hemodinámica

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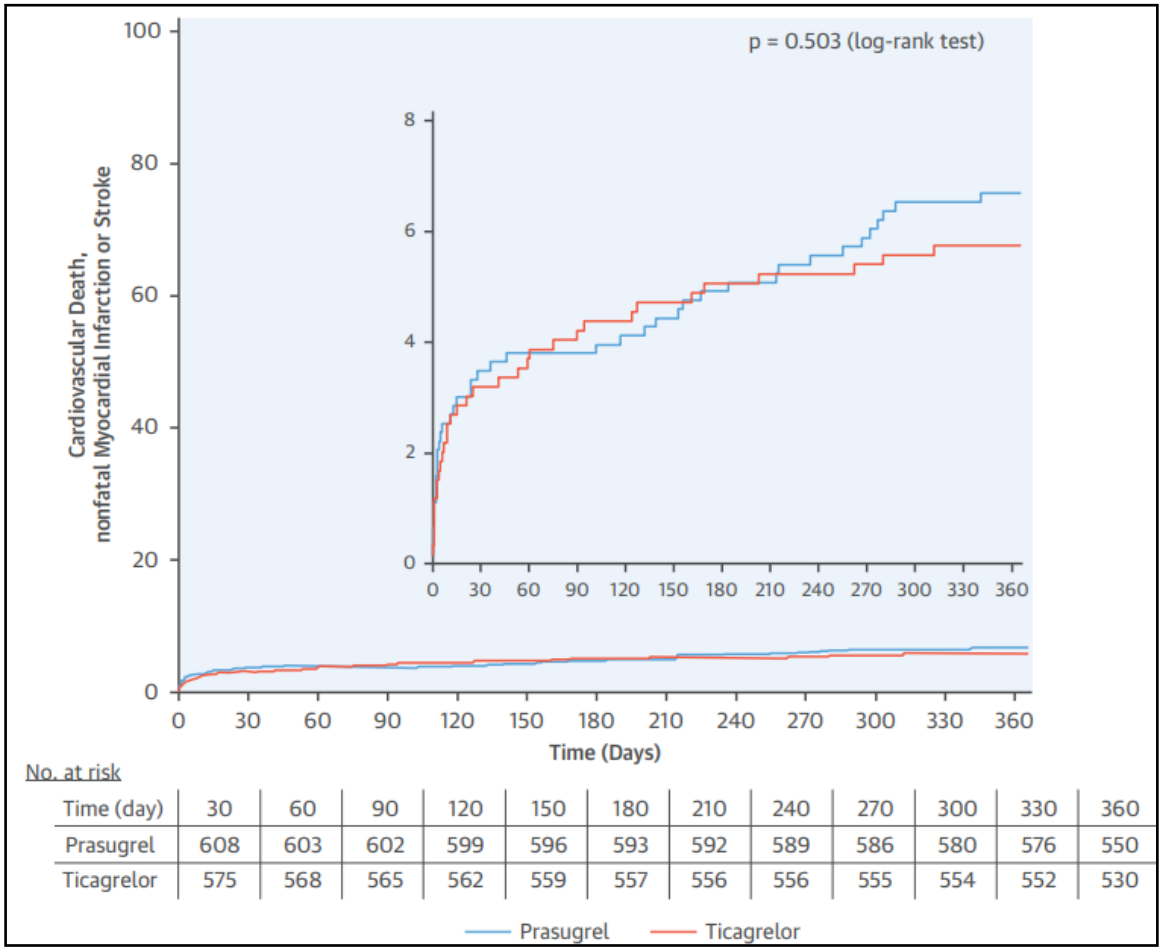
Diciembre, 2019

¿Ticagrelor o prasugrel?

A favor de Ticagrelor	A favor de Prasugrel
Se puede administrar en ACV previo	Una sola toma (adherencia)
No se modifica en función del peso/edad	No asocia “disnea” o trastornos de conducción
Se puede administrar en manejo conservador	⬇ Reinfarto como endpoint individual
Se puede administrar al ingreso en IAMSEST	No interacciones con dosis de aspirina
Se puede administrar sin conocer la anatomía coronaria	No variaciones regionales significativas
Más rápido “off-set” (3-5 días vs 7 días)	
⬇ mortalidad como endpoint individual	
Efecto beneficioso a 3 años (60mg/12h)	
Se dispone de forma bucodispersable	

PRAGUE 18



Time (day)	30	60	90	120	150	180	210	240	270	300	330	360
Prasugrel	608	603	602	599	596	593	592	589	586	580	576	550
Ticagrelor	575	568	565	562	559	557	556	556	555	554	552	530

- N=1230 (95% STEMI)
- High incidence of switching to clopidogrel after discharge 34-44%.
- Premature termination of enrollment (futility).
- AMI type 4a not considered. Superiority of ticagrelor over prasugrel (sample size).

J Am Coll Cardiol. 2018 Jan 30;71(4):371-381

Diseño

- Investigator initiated, phase 4, multicenter, randomized, open-label trial.
- Deutsches Herzzentrum München in Munich, Germany.
- SCA de cualquier tipo con estrategia invasiva planeada.
- Criterios de exclusión derivados de FT de productos.
- Randomization ratio of 1:1.
- *Primary end point:* death, myocardial infarction, or stroke at 1 year after randomization.
- *Secondary end point:* included the safety end point (BARC 3-5, stent thrombosis, individual components of PE).

Tamaño muestral

STATISTICAL ANALYSIS

The sample-size calculation was based on the assumption that the incidence of the primary end point would be 10.0% in the ticagrelor group[4] and 12.9% in the prasugrel group. With this assumption, we calculated that 1895 patients in each group would be needed for the trial to have 80% power to detect a relative risk that was lower by 22.5% in the rate of the primary end point in the ticagrelor group as compared with the prasugrel group with the use of a two-sided alpha level of 0.05, according to a chi-square test. Compensation for censoring of data for patients who were lost to follow-up required enrollment of 4000 patients.

Resultados

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)
Age — yr	64.5±12.0	64.6±12.1
Female sex — no. (%)	478 (23.8)	478 (23.8)
Cardiovascular risk factors — no./total no. (%)		
Diabetes	463/2011 (23.0)	429/2005 (21.4)
Use of insulin for diabetes	143/2011 (7.1)	137/2005 (6.8)
Current smoker	682/2002 (34.1)	667/1999 (33.4)
Arterial hypertension	1432/2008 (71.3)	1384/2003 (69.1)
Hypercholesterolemia	1178/2007 (58.7)	1163/2003 (58.1)
Medical history — no./total no. (%)		
Myocardial infarction	311/2010 (15.5)	320/2005 (16.0)
PCI	453/2011 (22.5)	463/2004 (23.1)
Aortocoronary bypass surgery	115/2011 (5.7)	130/2005 (6.5)
Cardiogenic shock — no. (%)	31 (1.5)	34 (1.7)
Blood pressure — mm Hg		
Systolic†	144±25	143±24
Diastolic‡	82±15	82±14
Heart rate — beats/min§	77±16	76±16
BMI¶	27.8±4.6	27.8±4.4
Weight <60 kg — no./total no. (%)	108/2003 (5.4)	94/1988 (4.7)
Creatinine level — μmol/liter‖	88±27	88±31
Diagnosis at admission — no. (%)		
Unstable angina	249 (12.4)	261 (13.0)
NSTEMI	930 (46.2)	925 (46.1)
STEMI	833 (41.4)	820 (40.9)
Coronary angiography — no. (%)	2003 (99.6)	2001 (99.8)
Treatment strategy — no./total no. (%)**		
PCI	1676/2009 (83.4)	1701/2005 (84.8)
CABG	47/2009 (2.3)	36/2005 (1.8)
Conservative therapy	285/2009 (14.2)	268/2005 (13.4)
Other††	1/2009 (<0.1)	0

Resultados

- 62-63% acceso femoral.
- DES ≈ 90%.
- Heparina sódica ≈ 93-94%.
- Inhibidores Gp IIb-IIIa ≈12-13%.
- SCA de cualquier tipo con estrategia invasiva planeada.
- Al alta: 83% BB, 84% ACEi/ARB, 92% statins.

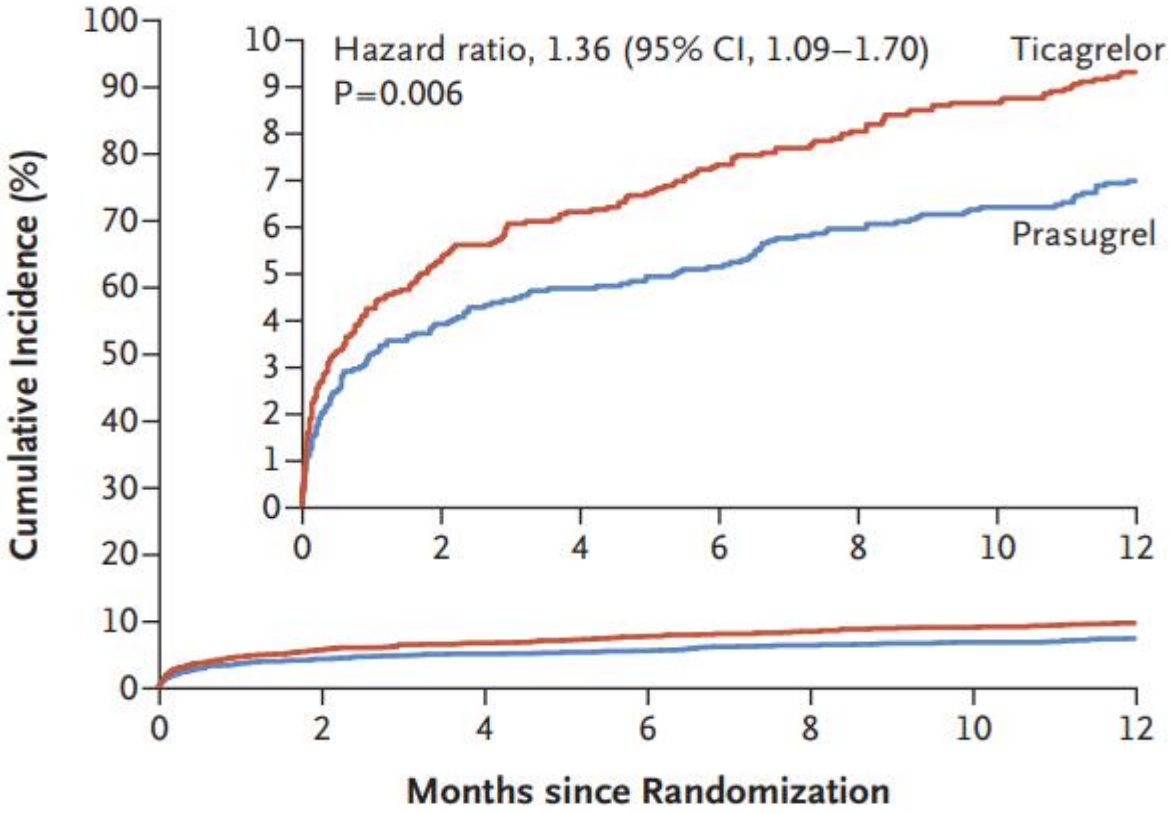
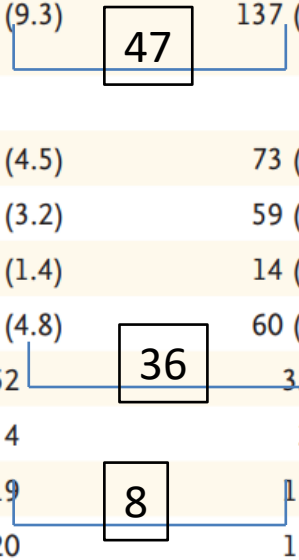


Figure 2. Cumulative Incidence of the Primary End Point at 1 Year.

The Kaplan–Meier curves show the cumulative incidence of the primary end point, which was a composite of death, myocardial infarction, or stroke at 1 year. The inset shows the same data on an enlarged y axis.

End Point	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)	Hazard Ratio (95% CI)	P Value
Primary end point: death, myocardial infarction, or stroke — no. (%)	184 (9.3)	137 (6.9)	1.36 (1.09–1.70)	0.006
Death — no. (%)				
From any cause	90 (4.5)	73 (3.7)	1.23 (0.91–1.68)	
From cardiovascular cause	63 (3.2)	59 (3.0)		
From noncardiovascular cause	27 (1.4)	14 (0.7)		
Myocardial infarction — no. (%)†	96 (4.8)	60 (3.0)	1.63 (1.18–2.25)	
Type 1 — no.	52	35		
Type 2 — no.	4	3		
Type 4a — no.	19	11		
Type 4b — no.	20	11		
Type 5 — no.	1	0		
STEMI — no.	31	14		
Stroke				
Any — no. (%)	22 (1.1)	19 (1.0)	1.17 (0.63–2.15)	
Ischemic — no.	16	17		
Hemorrhagic — no.	6	2		



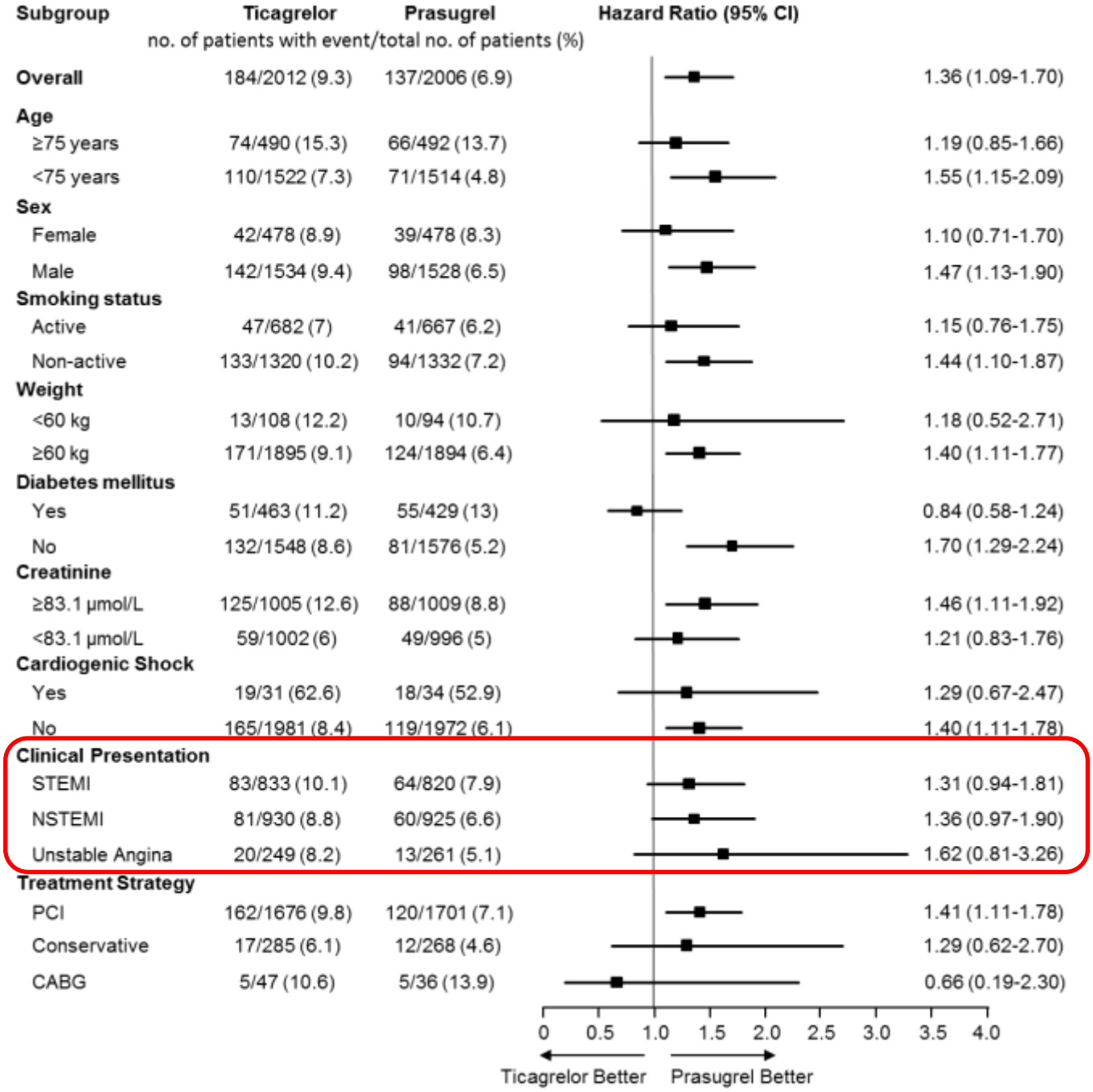
N Engl J Med. 2019 Oct 17;381(16):1524-1534

Definite or probable stent thrombosis — no. (%)	26 (1.3)	20 (1.0)	1.30 (0.72–2.33)	
Definite stent thrombosis — no. (%)	22 (1.1)	12 (0.6)		
Secondary safety end point: BARC type 3, 4, or 5 bleeding — no./total no. (%)‡	95/1989 (5.4)	80/1773 (4.8)	1.12 (0.83–1.51)	0.46
BARC 3a	47	41		
BARC 3b	32	31		
BARC 3c	4	2		
BARC 4	8	2		
BARC 5a	1	0		
BARC 5b	3	4		

10

15

N Engl J Med. 2019 Oct 17;381(16):1524-1534


Subgroup
Ticagrelor
Prasugrel
Hazard Ratio (95% CI)
no. of patients with event/total no. of patients (%)
Overall 184/2012 (9.3) 137/2006 (6.9) 1.36 (1.09-1.70)
Age
≥75 years 74/490 (15.3) 66/492 (13.7) 1.19 (0.85-1.66)
<75 years 110/1522 (7.3) 71/1514 (4.8) 1.55 (1.15-2.09)
Sex
Female 42/478 (8.9) 39/478 (8.3) 1.10 (0.71-1.70)
Male 142/1534 (9.4) 98/1528 (6.5) 1.47 (1.13-1.90)
Smoking status
Active 47/682 (7) 41/667 (6.2) 1.15 (0.76-1.75)
Non-active 133/1320 (10.2) 94/1332 (7.2) 1.44 (1.10-1.87)
Weight
<60 kg 13/108 (12.2) 10/94 (10.7) 1.18 (0.52-2.71)
≥60 kg 171/1895 (9.1) 124/1894 (6.4) 1.40 (1.11-1.77)
Diabetes mellitus
Yes 51/463 (11.2) 55/429 (13) 0.84 (0.58-1.24)
No 132/1548 (8.6) 81/1576 (5.2) 1.70 (1.29-2.24)
Creatinine
≥83.1 µmol/L 125/1005 (12.6) 88/1009 (8.8) 1.46 (1.11-1.92)
<83.1 µmol/L 59/1002 (6) 49/996 (5) 1.21 (0.83-1.76)
Cardiogenic Shock
Yes 19/31 (62.6) 18/34 (52.9) 1.29 (0.67-2.47)
No 165/1981 (8.4) 119/1972 (6.1) 1.40 (1.11-1.78)
Clinical Presentation
STEMI 83/833 (10.1) 64/820 (7.9) 1.31 (0.94-1.81)
NSTEMI 81/930 (8.8) 60/925 (6.6) 1.36 (0.97-1.90)
Unstable Angina 20/249 (8.2) 13/261 (5.1) 1.62 (0.81-3.26)
Treatment Strategy
PCI 162/1676 (9.8) 120/1701 (7.1) 1.41 (1.11-1.78)
Conservative 17/285 (6.1) 12/268 (4.6) 1.29 (0.62-2.70)
CABG 5/47 (10.6) 5/36 (13.9) 0.66 (0.19-2.30)
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Ticagrelor Better
Prasugrel Better

Aspectos críticos

1. El estudio compara dos fármacos y dos estrategias distintas (SCA no ST elevado).

2. Mientras que la tasa de eventos del brazo de ticagrelor en ISAR-REACT fue similar a PLATO (9,3 vs 10,2%), aquella en el brazo de prasugrel fue muy inferior en ISAR-REACT vs. TRITON (6,9 vs 10,7%).

3. La diferencia absoluta de riesgo entre prasugrel y ticagrelor es 2,3% es incluso mayor que la observada frente a clopidogrel en TRITON (2,2%) y PLATO (1,9%), o frente a placebo en CURE (2,1%).

Aspectos críticos

4. Ensayo clínico “abierto” (no doble ciego).

5. Seguimiento telefónico 83% pacientes, 7% “por carta”. 90 pacientes se perdieron en el seguimiento a 1 año.

6. Elevada proporción de “cross-over” al alta (≈20%, ≈400 pacs) y discontinuación del tratamiento a 1año (15,2 y 12,5%, tica y prasu, 243 y 199 pacs). 1 año: 32,4% prasu arm & 30,4% tica arm no recibieron la medicación del estudio.

   In a post-hoc on-treatment analysis, there was no significant difference between ticagrelor and prasugrel for the primary endpoint (HR, 1.34; 95% CI, 0.98-1.82).

4. “Randomization with sealed envelopes”.

Ensayo ENTRUST-AF PCI

All patients who were assigned to a group were followed for 12 months after randomisation and every effort was made to complete the clinical follow-up. For this purpose, onsite visits could be replaced by telephone contact at the patient's request, and clinical follow-up information was collected from hospital records and national death registries unless explicitly forbidden by the patient. Trial medications were dispensed every 3 months.

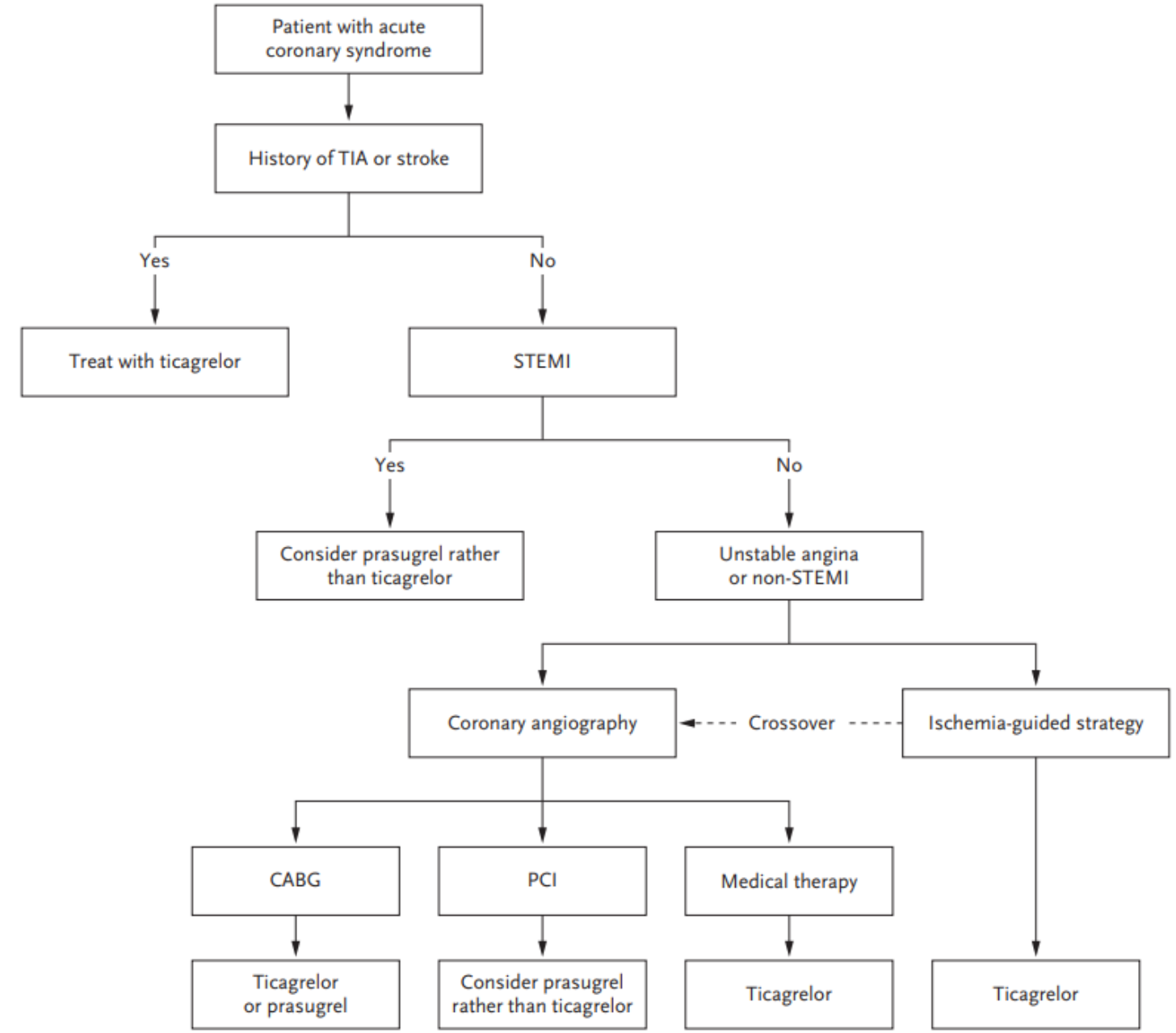
Adherence was assessed by direct pill counts and self-reporting. Adherence counselling by the study team was the default strategy to improve drug adherence.

Clinical follow-up of the patient was conducted through onsite visits at 1, 3, 6, 9, and 12 months after randomisation, and telephone assessments at 2, 4, 5, 7, 8, 10, and 11 months after randomisation.[14] A tabular summary of the visits scheduled and a description of follow-up procedures is in the appendix (pp 17–19).

Lancet. 2019 Oct 12;394(10206):1335-1343

Aspectos críticos

8. A disproportionate number of patients were excluded from the safety analysis in the prasugrel arm (233/2006, 11.6%) compared to the ticagrelor arm (23/2012, 1.1%), with no additional explanation.



eBakey Veterans

Figure 1. Proposed Algorithm for the Choice of an Oral $P2Y_{12}$ Receptor Inhibitor for Patients with an Acute Coronary

tive surgery to offset its longer-lasting antiplatelet effects (7 days, vs. 3 to 5 days). Unlike ticagrelor,[10] the long-term benefits of prasugrel beyond 1 year and its use as part of a dual-therapy strategy in patients who have acute coronary syndromes and atrial fibrillation are not well studied.

Overall, although long-term data and additional comparative-effectiveness data are lacking, prasugrel has now become the $P2Y_{12}$ receptor inhibitor of choice in patients with acute coronary syndromes (Fig. 1). It should be used instead of ticagrelor in appropriately selected patients with this condition.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Division of Cardiology, Baylor College of Medicine, and the Michael E. DeBakey Veterans Affairs Medical Center — both in Houston.

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics — 2019 update: a report from the American Heart Association. Circulation 2019;139(10):e56-e528.
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

Ticagrelor or Prasugrel in Acute Coronary Syndromes — The Winner Takes It All?

Hani Jneid, M.D.

Orville Wright said, "If we all worked on the assumption that what is accepted as true is really true, there would be little hope of advance." Approximately one person in the United States has a myocardial infarction every 40 seconds, and more than 1 million coronary events occur each year, of which one third are recurrent events.[1] Antiplatelet medications and strategies to lower

In the Study of Platelet Inhibition and Patient Outcomes (PLATO), ticagrelor was superior to clopidogrel in reducing the incidence of the composite cardiovascular outcome (death from vascular causes, myocardial infarction, or stroke) after an acute coronary syndrome, with no increase in the safety end point of major bleeding. However, there was an increase in the rate of

Division of Cardiology, Baylor College of Medicine, and the Michael E. DeBakey Veterans Affairs Medical Center, both in Houston.

“If we all worked on the assumption that what is accepted as true is really true, there would be little hope of advance”

Orville Wright

Conclusiones

1. El estudio ISAR-REACT 5 presenta importantes limitaciones metodológicas que hacen difícil su interpretación.

2. En el estudio ISAR-REACT 5 los pacientes con síndrome coronario agudo remitidos para intervencionismo coronario y tratados con prasugrel experimentaron menos infartos de miocardio en el seguimiento.

Conclusiones

3. El efecto beneficioso de prasugrel fue evidente para los infartos tipo 1 y tipo 4a sobretodo.

4. El beneficio de prasugrel sobre ticagrelor fue aparentemente homogéneo en función del tipo de síndrome coronario agudo.

Conclusiones

5. Si, los resultados del ensayo ISAR-REACT 5 son capaces de modificar la práctica clínica y/o las guías de práctica clínica es difícil de predecir, dadas las limitaciones mencionadas en la presentación.

6. Los pacientes tratados con stent y prasugrel presentaron menos trombosis definitiva, aún no significativamente.